REMARKS

This Response is filed in connection with the final Office Action mailed August 31, 2005. In the Office Action, the Examiner stated that the Amendment and Response Under 37 C.F.R. § 1.111, filed on February 2, 2005, has been entered. Applicants make no amendments to the presently pending claims at this time. Thus, claims 13-16, 26 and 27 are currently pending in the application. No new matter has been introduced.

I. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

The Examiner has rejected claims 13, 15-16 and 26-27 for lack of written description under 35 U.S.C. § 112, 1st ¶, for the alleged failure of the disclosure to provide an adequate written description, the reasons for which are set forth in the current and previous Office Actions.[1] Applicants respectfully submit that the rejection is erroneous because (1) the Examiner appears to have consistently mischaracterized the nature of the invention; (2) the Examiner has misapplied the legal standard for written description under § 112, 1st ¶; and (3) the claimed invention is adequately described.

A. The Invention is Mischaracterized

The Examiner contends that there is a lack of written description for "a method for genus of nucleic acid [sic] whose function is not known."[2] Further, the Examiner states that the "essential feature of the claimed method is the discovery that nucleic acid sequences which have not been identified by function such as SEQ ID NO:1 can be used as regulated sequence of the estrogen modulation but the function of SEQ ID NO:1 is not known."[3] Applicants respectfully submit that this is a mischaracterization of the present invention. The "discovery" is *not* the "method for genus nucleic acids whose function is not known," as the Examiner contends. Rather, the presently claimed invention is directed to the

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[1] *See*, August 31, 2005 Office Action at pp. 2-3; November 2, 2005 Office Action at pp. 2-3; March 25, 2003 Office Action at pp. 2-3; and October 21, 2003 Office Action at pp. 2-3.

[2] August 31, 2005 Office Action at p. 3.

[3] *Id.* In support of this argument, the Examiner cites to the nucleic acid sequence identified by NCI-CGAP accession number AA747315 (1999) (corresponding to SEQ ID NO:1) and alleges that this sequence resulted from a human genome sequencing and that "the function of the sequence is not known." *Id.*

discovery that certain genes, referred to as estrogen-regulated markers ("ERMs"), previously identified and sequenced in the prior art, are *now* characterized by function, *i.e.*, they have been definitively shown by Applicants to be regulated by estrogen (*i.e.*, their expression is either increased or decreased in response to estrogen treatment).

As such, the claimed assays are based on Applicants' discovery that these ERMs are useful to identify/screen for compounds that have estrogenic and/or anti-estrogenic activity (*i.e.*, selective estrogen receptor modulators, or "SERMs") for use in preventing or treating, *inter alia,* cardiovascular disease, osteoporosis and cancer (*e.g.*, breast cancer). *See, e.g.*, pp. 1-2 and 16-17 of the originally filed specification. According to the claimed method, SERMs are identified by their ability to modulate the expression level of an ERM, a gene whose expression level is altered (*i.e.*, increased or decreased) in response to estrogen in particular cells that express the estrogen receptor (ERα and/or ERβ). *See* p. 8 of originally filed specification and currently pending claim 13. As disclosed in Example 2 and Table I of the originally filed specification at pp. 56-68, over 75 ERMs were identified to be responsive to estrogen (17-β estradiol) in ERα-positive vascular endothelial cells (VE-ERα cells).[4]

B. <u>The Legal Standard for Written Description is Misapplied</u>

Applicants respectfully submit that the Examiner has misapplied the legal standard for written description under § 112, 1st ¶. In particular, Applicants note that the Examiner has inappropriately couched his rejection in terms of enablement, by stating that "[c]laims 13, 15-16 and 26-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to *enable* one skilled in the art to which it pertains, or with which it is most nearly connected, *to make and/or use* the invention (emphasis added)."[5] Although the Examiner concludes that this is a written description rejection, Applicants respectfully submit that the rejection, as written, is an *enablement* rejection. Applicants respectfully remind the Examiner that the written description requirement is *separate and distinct* from the enablement requirement. *See University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 921-22 (Fed. Cir. 2004)

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[4] The Incyte UniGEM technology was used to survey the panel of genes and to establish the estrogen-regulated gene profile of the VE-ERα cells treated for 6 hours with 17-β estradiol or vehicle control (ethanol). UniGem V contains approximately 8500 human sequences including both known genes and expressed sequence tags (ESTs). *See* originally filed specification at pp. 56-57.

[5] See FN 1, *supra.*

("[t]he United States Supreme Court also recently acknowledged written description as a statutory requirement distinct not only from the best mode requirement, but also from enablement...[a]lthough there is often significant overlap between the three requirements, they are nonetheless independent from each other" (citations omitted)). *See also* MPEP § 2163 (Rev. 3, August 2005) at pp. 2100-171-72. Toward this end, Applicants respectfully submit that the appropriate question for determining adequate written description is whether the claims contain subject matter which was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application as filed, had *possession* of the claimed invention. *See, e.g.*, MPEP § 706.03(c) (Rev. 3, Aug. 2005) at p. 700-70; and *infra*.

Applicants remind the Examiner that the legal standard for the written description requirement has been set forth by the Circuit. *See University of Rochester*, 358 F.3d at 921-23; *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d. 1306, 1319-21 (Fed. Cir. 2003); *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67 (Fed. Cir. 1997); and *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1560-64 (Fed. Cir. 1991). Indeed, much of this case law on the written description requirement has in large part been adopted in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, Fed. Reg. Vol. 66, No. 4 at pp. 1099-1111 (January 5, 2001), hereinafter, "Written Description Guidelines"; and MPEP § 2163 (Rev. 3, Aug. 2005).

To satisfy the written description requirement, an applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.*" *Vas-Cath*, 935 F.2d at 1563-64 (emphasis in original) and MPEP § 2163 at p. 2100-172. Possession may be shown in a variety of ways, including description of an actual reduction to practice, disclosure of "sufficiently detailed, relevant identifying characteristics," *i.e.*, "***complete or partial structure***, other physical and/or chemical properties, ***functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics***" (emphasis added). MPEP § 2163 at 2100-178-79. *See also Enzo Biochem., Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002) (quoting Written Description Guidelines). Further, for some biomolecules, examples of identifying characteristics include "***sequence***, structure, binding affinity, binding specificity, molecular weight, and length (emphasis added). MPEP § 2163 (Rev. 3, Aug. 2005) at p. 2100-179.

Moreover, in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997)[6], the Federal Circuit held that an "adequate written description of a DNA...'requires a precise definition, such as by ***structure***, formula, chemical name, or physical properties,'...what is required is a description [*i.e.*, sequence] of the DNA itself" (emphasis added). *Lilly*, 119 F.3d at 1566-67. In the case, the Federal Circuit agreed with Eli Lilly that UC's generic claims to a cDNA encoding mammalian and vertebrate insulin were invalid for lack of written description because description of one species of a genus (in this case, rat) did not necessarily describe the entire genus. *Lilly* at 1567-68. In other words, a description of rat insulin cDNA is not a description of the broad classes of vertebrate or mammalian cDNAs which include human insulin cDNA. The court held that a "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, ***defined by nucleotide sequence***, falling within the scope of the genus..." (emphasis added). *Id.* at 1569. Thus, *Lilly* makes clear that although function alone may not be sufficient to describe a claimed genus, the ***nucleotide sequence*** of each of the individual species of a genus is adequate for purposes of satisfying the written description requirement under 35 U.S.C. § 112, 1st ¶.

C. The Claimed Invention is Adequately Described

Applicants have fully satisfied the written description requirement of § 112, 1st ¶, by disclosing the nucleotide sequence of at least 75 ERMs identified to be responsive to estrogen using the methods disclosed in the present application. Under the legal standard for written description, outlined above, such a disclosure of structure (sequence), coupled with function (ability to be regulated by estrogen), is clearly sufficient.

In contrast to the situation in *Lilly*, the present application fully satisfies the written description requirement of § 112, 1st ¶, by disclosing the nucleotide sequences of the genus of ERMs that have been identified to be responsive to estrogen (*see* Example 2 and Table I therein). It is emphasized that Applicants are not claiming the ERMs themselves (*i.e.*, the nucleotide sequences of SEQ ID NOS:1-19), but are claiming an assay to identify compounds (*i.e.*, SERMS) which modulate expression of the ERMs. Such ERMs were identified by Applicants to be regulated by estrogen in the experiment described in Example

[6] Applicants note that the *Lilly* case was cited by the Examiner in the March 25, 2003 Office Action at pp. 2-3 for essentially the same argument ("[t]hus, the disclosure does not have written description for the large genus of estrogen regulated marker. One skilled in the art cannot envision all the estrogen-regulated markers").

2. Moreover, the specification discloses the nucleotide sequence, *i.e.*, structure, of at least 75 examples of ERMs that may be used in accordance with the claimed assays (*see, e.g.*, Example 2 and Table I). Under *Lilly* and the Federal Circuit case law described above, such a description of sequence, coupled with function, is *clearly sufficient* to show that Applicants were in possession of the invention at the time the application was filed.

Moreover, the Examiner's citation to the nucleic acid sequence identified by NCI-CGAP accession number AA747315 (1999) (corresponding to SEQ ID NO:1) for the argument that such an alleged "orphan protein whose function is not known" establishes an insufficient disclosure, is equally misplaced. The Examiner's citation to a sequence, a mere recitation of SEQ ID NO:1, without more, is not evidence contrary to the function attributed to SEQ ID NO:1 by Applicants. As such, SEQ ID NO:1, notwithstanding the 1999 citation, has been definitively shown by Applicants (just like SEQ ID NOS:2-19) to be regulated by estrogen. Indeed, all of these ERM sequences are characterized by function, and the Examiner has provided absolutely no evidence to the contrary, *i.e.*, that the ERMs described in the present application are not regulated by estrogen. The Examiner therefore has provided no evidence that the ERMs disclosed herein are not functional or that they are orphan proteins.

For the foregoing reasons, Applicants respectfully request that the rejection of claims 13, 15-16 and 26-27 under 35 U.S.C. § 112, 1st ¶, for lack of written description, be withdrawn.

II. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH FOR LACK OF ENABLEMENT, SHOULD BE WITHDRAWN

The Examiner has introduced a rejection of claims 13-16 and 26-27 for lack of enablement under 35 U.S.C. § 112, 1st ¶. In particular, the Examiner states that the specification, while being enabling for a "method of using estrogen receptor [sic] marker with function, does not reasonably provide the full scope of enablement for a method of using an estrogen receptor [sic] marker which is an orphan protein."[7] The Examiner alleges that the specification does not teach how to use "peptide fragments, substantial equivalents, or modified peptide derivatives fragments of estrogen receptor marker which are not functional."[8] The Examiner contends that one of skill in the art could not predict the tertiary

[7] August 31, 2005 Office Action at pp. 3-4.

[8] *Id.*

structure of an orphan protein using the primary amino acid sequence of a polypeptide alone, whose function is not known. Applicants respectfully assert that the Examiner is in error, and that the requirement for enablement 35 U.S.C. § 112, 1st ¶, has been fully satisfied. As such, the rejection should be withdrawn for the reasons detailed below.

The Examiner is respectfully reminded that the legal test for enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *See* MPEP § 2164.01, Rev. 3, August 2005; and *U.S. v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). Factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) and MPEP § 2164.01(a) at p. 2100-193. Further, a "patent need not teach, and preferably omits, what is well known in the art." *In re Buchner*, 929, F.2d 660, 661 (Fed. Cir. 1991).

At the outset, Applicants submit that Example 4, *inter alia*, is a working example of the claimed invention (*see, e.g.*, pending claim 13). ***As long as the specification "discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied"*** (emphasis added). *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970); MPEP § 2164.01(b) at p. 2100-194; and Example 4.

Moreover, Applicants submit that the specification is replete with methods to detect differential gene expression, both at the nucleic acid *and* protein level, in response to treatment with estrogen and/or a selective estrogen receptor modulator ("SERM"). Methods for measuring nucleic acids (*e.g.*, mRNA, cDNA or DNA) of estrogen-responsive genes include, but are not limited to, the use of gene chips (*e.g.*, the UniGEM technology; *see* pp. 11-12; and Example 2 of the originally filed specification); reporter gene assays where a gene encoding an ERM or ERM-related protein is isolated and linked to various operably linked reporter genes (*e.g.*, luciferase, CAT; *see* pp. 14-15); RNase protection assays (*see* p. 18); and PCR (*see* p. 26). Indeed, Example 4 of the present application is a working example that

discloses the use of ERMs identified by the methods of the invention (*see, e.g.*, Example 2) for identifying agents with estrogenic activity using an RNase protection assay (pp. 70-72).

The specification also discloses methods to detect protein expression in response to estrogen treatment. Such methods include, but are not limited to, recombinantly expressing a nucleic acid of the invention (*e.g.*, a nucleic acid encoding an ERM) to produce a polypeptide using recombinant techniques well-known to those skilled in the art (*see* pp. 27-38) and subsequent detection using antibody-based techniques such as ELISA and Western blot assays (*see* pp. 38-42). The specification provides multiple methods for recombinantly expressing a polypeptide of the invention in prokaryotic cells (*e.g.*, *E. coli*) and eukaryotic cells (*e.g.*, insect, yeast or mammalian cells). *See* pp. 29-34 of the originally filed specification. Furthermore, the specification incorporates by reference various references that teach recombinant expression of proteins (*e.g.*, Gottesman, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128; *see* p. 31 of the specification as filed).

Thus, recombinant expression of proteins was well known and routine to those of skill in the art of recombinant DNA and protein biology at the time the application was filed. Applicants have provided multiple working examples throughout the specification of how to make and use the invention (*i.e.*, how to identify SERMs which regulate the expression of ERMs in an assay; *see, e.g.*, Examples 1-4). Thus, the inventors provided clear direction and many working examples of how to practice the *claimed* invention. The state of the art (*i.e.*, recombinant DNA and protein biology) at the time the application was filed allowed one of skill in the art to make and use the claimed invention using the well known techniques taught in the specification without performing further experimentation. As such, contrary to the Examiner's allegations, the specification fully enables one to make and use the full scope of the claimed invention without undue experimentation. Indeed, the Examiner has provided no evidence that the large number of species disclosed in the instant invention are not functional. To the contrary, the Examples provided in the specification, *e.g.*, Examples 2-4, definitively demonstrate that these ERMs are regulated by estrogen.

Applicants further submit that the Examiner unduly focuses on the protein structure and function of the ERMs disclosed in the specification. The Examiner's primary concern seems to be that a primary amino acid sequence alone, derived from a nucleotide sequence of a protein, such as an orphan protein allegedly provided by the specification, does not allow one of skill in the art to predict the tertiary structure of the protein, especially if it is "truncated" and does not fold properly. To support his allegations, the Examiner cites Bowie

et al., 1990, "Deciphering the Message in Protein Sequence: Tolerance to Amino Acid Substitutions," *Science* 247:1307-10 ("Bowie").

First, Applicants submit that Bowie is not evidence that the ERMs disclosed in Table I of Example 2 in the specification have no activity. None of the ERMs in Table I are even discussed in Bowie. Second, Applicants note that Bowie is dated over *ten years* before the filing date of the subject application. Thus, it is not likely to reflect the state of the art at the time the application was filed, which is the relevant time period for determining enablement (*see* MPEP § 2164.05(a) at p. 2100-199: "[t]he state of the prior art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date"). Further, it is likely that the state of the art of protein science, in particular, prediction of protein structure, is rapidly evolving, and a reference published closer to Applicants' filing date might have more force and effect.

Nonetheless, Bowie teaches that comparison of different sequences from related proteins can reveal key features, such as hydrophobic residues, which may improve the understanding of how a particular protein folds (its tertiary structure) and how it performs its function. Further, by studying patterns of tolerance to amino acid substitutions of varying hydrophobicity, one can identify residues likely to be buried in a protein inside a pocket or those likely to occupy surface positions. Such information based on related sequences can be used to develop algorithms to predict the tertiary structure of particular proteins from a given sequence. Such a reference, however, cannot support the Examiner's bare assertion that Applicants have not enabled one of skill in the art how to make and use the presently claimed invention, which is an assay to identify compounds (SERMs) that have estrogenic and/or antiestrogenic activity and which modulate the expression levels of at least one estrogen-regulated marker (ERM). Bowie neither describes nor suggests that the ERMs of the present application are not functional or are orphan proteins.

For the foregoing reasons, Applicants submit that the Examiner's rejection for lack of enablement is improper and should be withdrawn.

III. THE REJECTION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The Examiner has maintained the rejections of claims 13-16, 26 and now claim 27, which are drawn to methods for identifying a SERM, as being anticipated by Mendelsohn *et al.* (U.S. Patent No. 5,728,534, issued March 17, 1998) ("Mendelsohn"), the

reasons for which are set forth in the current and previous Office Actions[9]. In particular, the Examiner contends that Mendelsohn teaches the screening assays of the instant invention, and that all the limitations of the claims are taught by Mendelsohn. Applicants submit that this rejection is erroneous for the reasons detailed below and should be withdrawn.

Applicants respectfully remind the Examiner that a claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (see, *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the...claim" (*see*, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)). *See also* MPEP § 2131 (Rev. 3, Aug. 2005). Applicants submit that for the reasons detailed below, Mendelsohn does not satisfy the requirement for anticipation as set forth by the Federal Circuit.

The presently claimed invention relates to assays for identifying a selective estrogen receptor modulator (SERM) which modulates the expression of one or more estrogen-regulated markers (ERMs) identified to be responsive to estrogen in the examples provided in the originally filed specification (*see* discussion of ERMs and SERMs above). The cells to be used in the claimed assays include, *inter alia*, cells of the reproductive system such as breast, ovarian and endometrial cells (*see*, *e.g.*, pending claims 16 and 26). An essential feature of the claimed assay is the requirement that a candidate agent (*i.e.*, a candidate SERM) *does have an effect* on these cells, whether it is an estrogenic or anti-estrogenic effect (*e.g.*, an increase or decrease in the expression of one or more ERMS disclosed in Table I, respectively).

Mendelsohn, in contrast, discloses methods which can be used to identify "vasoprotective agents." Mendelsohn at **1**:42-52. Mendelsohn teaches that a "preferred agent would inhibit the proliferation of vascular smooth muscle cells and/or increase proliferation of vascular endothelial cells associated with the development of atherosclerosis, but *not* have any significant effect on cells of the reproductive system, *e.g.*, breast cells or uterine cells" (emphasis added). Mendelsohn at **1**:58-63. Mendelsohn does not teach assays for identifying SERMS having an estrogenic and/or antiestrogenic effect on an ERM. As such, the claimed invention requires the opposite effect disclosed in Mendelsohn.

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[9] *See*, August 31, 2005 Office Action at p.5; November 2, 2005 Office Action at p.4; March 25, 2003 Office Action at pp. 3-4; and October 21, 2003 Office Action at pp. 3-4.

Further, while the claimed invention assays the activity of a single group of cells, the screening assay taught by Mendelsohn requires the simultaneous use and direct comparison in a single assay of ***two different groups of cells*** (*i.e.*, vascular/vascular, vascular/null or vascular/non-vascular) expressing an estrogen-responsive reporter gene to screen for vasoprotective agents. In particular, the reference teaches that:

> there are three preferred formats for a screening assay which is based on an estrogen responsive reporter. All three formats involve *at least two different cell types* which harbor the same estrogen responsive reporter. The preferred assays use either *vascular cells and non-vascular cells or vascular cells and null cells or two different types of vascular cells*...The use of two different cell lines of the same type in a single assay format is desirable because one can identify candidate vasoprotective agents which have the same or similar effect on several cells of the same type.

Mendelsohn at **13:**1-20. Indeed, one cell type used in an assay taught by Mendelsohn must *always* be a vascular cell. The other cell type could either be another type of vascular cell, a null cell or a non-vascular cell.

In contrast, the claimed invention does not relate to the simultaneous use and direct comparison of two groups of cells of different cell types in a single assay to determine whether or not a candidate agent is a SERM. Rather, the claimed assays of the instant invention are directed to the comparison of the levels of ERM expression in a single group of cells before and after contact with a candidate agent, wherein the levels of ERM expression are determined in the same cells in the same assay; the only difference is that the levels are measured in the presence or absence of a candidate agent. There is no direct comparison between two groups of cells of different cell types in a single assay, as described by Mendelsohn. As such, Mendelsohn cannot teach or even suggest the claimed methods.

Furthermore, Applicants have set forth and claim various methods to detect ERM expression in response to treatment with a candidate SERM, including RNase protection, Western blot analysis, ELISA, as well as reporter gene assays (claim 27). Mendelsohn does not teach nor claim these methods.

Accordingly, Applicants respectfully submit that the Examiner has mischaracterized Mendelsohn because the reference does not set forth "each and every element" as set forth in the present claims. Therefore, Mendelsohn cannot form the basis of a proper rejection of the present claims under 35 U.S.C. § 102(b).

Applicants respectfully request that, for the foregoing reasons, the anticipation rejection of claims 13-16 and 26-27 be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks intended to put the claims in form for allowance. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned at (212) 326-3939, if a telephone call could help resolve any remaining items.

Respectfully submitted,

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Date: November 29, 2005

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